REMARKS

This amendment is filed in response to the final Office Action dated October 3, 2005 and is provided further to the Notice of Appeal filed February 1, 2006, the Appeal Brief filed June 19, 2006, and further to the amendment filed October 30, 2006. Applicants respectfully request that both the amendment filed October 30, 2006 and the present amendment be entered. Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and following remarks.

Upon entry of the amendment submitted on October 30, 2006, claims 36, 43, and 66-70 are pending and under consideration. By the present amendment, claims 66, 69, and 70 are canceled, and new claim 71 is added. Claims 36 and 68 are amended. Applicants submit that these amendments do not include new matter and are supported by the specification and claims as originally filed. For example, the drug:lipid range of 0.3:1 (w/w) is supported by the description of the specific drug:lipid ratio of 0.3:1 provided in Figure 1, and the sphingomyelin:cholesterol molar ratio of 55:45 is described on page 3, lines 33-34. The drug:lipid ratio range of 0.2-0.3 (w/w) is supported by the description of the range of 0.1-0.5:1 in paragraph 33 of the application as filed, in light of the description of the specific drug:lipid ratios of 0.2:1 and 0.3:1 provided in Figure 1. Applicants respectfully submit that numerical range limitations are considered adequately supported if they would be considered inherently supported by the discussion in the original disclosure. MPEP 2163.05. For example, in the decision in *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976), the ranges described in the original specification included a range of "25% - 60%" and specific examples of "36%" and "50%." Accordingly, a limitation to "between 35% and 60%" was considered supported and found to satisfy the written description requirement. The instant situation is analogous in that the claimed range is within the recited range and the specific recited values at either both ends of the range are described in the instant application.

It should also be noted that the above amendments are made without prejudice to prosecution of any subject matter removed or modified by amendment in a related divisional, continuation or continuation-in-part application.

Examiner Interview

Applicants wish to thank the Examiner for conducting a personal interview with Dr. Thomas D. Madden of Inex Pharmaceuticals Corp., the assignee of the instant application, and Dr. Carol D. Laherty, Applicants' representative in the instant application. It is Applicants' understanding that the Examiner would reconsider the patentability of claims reciting specific drug:lipid ratios in light of the discussions and evidence presented at the interview and believes that claims incorporating additional limitations could be allowable. The Examiner specifically suggested that claims that recite the drug:lipid ratio of 0.3:1 (w/w) and additional information evidencing the non-obviousness of the claimed formulations be submitted.

In accordance with the discussions at the interview and suggestions by the Examiner, by the present amendment, Applicants have amended claim 36 to recite that the drug:lipid ratio is in the range of 0.2 - 0.3:1 (w/w). This range is clearly demonstrated in the instant application to have superior pharmacokinetic properties as compared to formulations having lower drug:lipid ratios (Figure 1), and represents a narrow selection from within the broad ranges generally described in the prior art. In addition, new claim 71 is added to specifically recite one particular embodiment of the present invention exemplified in the instant application, wherein the drug:lipid ratio is about 0.3:1 (w/w), and the sphingomyelin:cholesterol molar ratio is about 55:45.

Rejection Under 35 U.S.C. §103

Claims 36, 43, and 66-68 stand rejected under 35 U.S.C. §103 as obvious over the combination of U.S. Patent No. 6,110,491 ("Kirpotin") and U.S. Patent No. 5,543,152 ("Webb").

Applicants respectfully submit that the instant claims are not obvious over the cited prior art, alone or in combination. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this basis of rejection in light of the amendments and remarks presented in the amendment submitted on October 30, 2006 and the present amendment.

Applicants submit that the presently claimed liposomal vinorelbine formulations, having a drug:lipid ratio in the range of 0.2-0.3:1 (w/w), have surprisingly enhanced drug retention properties *in vivo*, as compared to formulations having a lower drug:lipid ratio. As described in the Declaration of Dr. Thomas D. Madden submitted on October 30, 2006, it was an unexpected and surprising finding that liposomal vinorelbine formulations having a high vinorelbine:lipid ratio, *e.g.*, 0.2-0.3:1 (w/w) have enhanced drug retention as compared to those having lower drug:lipid ratios. As noted in Dr. Madden's declaration, this discovery contravenes the conventional understanding in the art at the time, which was that higher drug:lipid ratios result in more rapid drug release from liposomes.

Further to his previously submitted declaration, Dr. Madden submits with this amendment an additional declaration, which describes in further detail the surprising finding that liposomal vinorelbine formulations having the claimed high drug:lipid ratios have enhanced drug retention properties and associated therapeutic advantages. As described in this Declaration, it was the understanding in the prior art that during ion gradient-mediated drug loading, drug uptake into the liposome depleted the ion gradient, and that the greater the amount of drug taken up into the liposome, the more the ion gradient was depleted. Accordingly, liposomal drug formulations having a high drug:lipid ratio resulted in lower residual ion gradients than liposomal drug formulations having lower drug:lipid ratios. Since it is only the unprotonated form of vinorelbine that passes through the liposomal membrane, high residual ion gradients effectively maintain a greater amount of vinorelbine in the protonated form trapped in the liposome interior, while the lower residual ion gradients associated with high drug:lipid ratios result in a greater amount of unprotonated drug, which leaks from the liposome. Surprisingly, however, liposomal vinorelbine exhibits slower drug release at higher drug:lipid ratios, such as 0.2-0.3:1 (w/w). It was subsequently found that at these high drug:lipid ratios, a substantial

amount of the encapsulated vinorelbine is precipitated within the liposome's interior, resulting in its slow release from the liposome.

Applicants further note that the enhanced drug retention properties of the claimed liposomal vinorelbine formulations translate into superior pharmacokinetic and antitumor properties. As shown in the instant application and the accompanying Declaration of Dr. Thomas D. Madden, the claimed liposomal vinorelbine formulation, wherein the drug:lipid ratio is 0.3:1 (w/w) and the sphingomyelin:cholesterol molar ratio is 55:45, deliver more drug to tumors as compared to free vinorelbine and have enhanced anti-tumor activity as compared to free vinorelbine. These data further demonstrate the advantages of the claimed formulations.

Accordingly, the presently claimed invention, drawn to liposomal vinorelbine formulations having a high drug:lipid ratio of 0.2-0.3:1 (w/w), possesses surprising and unexpected advantages, which would not have been evident to one of skill in the art at the time the instant application was filed.

Furthermore, one of skill in the art, possessed with the understanding that higher drug:lipid ratios result in increased drug release, would not have been motivated to use the presently claimed high vinorelbine:lipid ratios, since slow drug release is generally considered a desired property in liposomal drug formulations. In addition, the prior art provides no motivation to achieve the specifically recited combination of features, *i.e.*, vinorelbine as the drug, the drug:lipid ratio of 0.2-0.3:1 (w/w), and liposomes comprising sphingomyelin and cholesterol. The selection of each of these specific features from the long laundry lists of drugs and potential lipids, as well as the broad drug:lipid ratios recited in the prior art is clearly not obvious, and nothing in the prior art point to the claimed combination of features. It is well-established that "the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." *In re Mills*, 916 F.2d 680 (Fed. Cir. 1990).

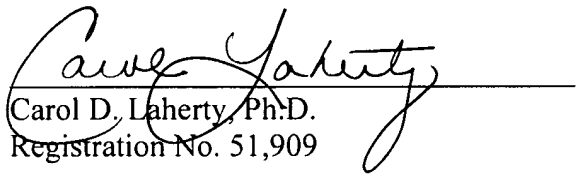
In light of these remarks, including those incorporated by reference from the appeal briefs and the accompanying Declaration establishing the existence of unexpectedly superior pharmacokinetic properties of the claimed liposomal compositions and associated clinical advantages, Applicants respectfully request that the Examiner reconsider and withdraw this basis of rejection.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants submit that all of the claims remaining in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. Should any issues remain prior to allowance, the Examiner is requested to contact the undersigned attorney at (206) 622-4900.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



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Declaration of Thomas D. Madden, Ph.D.

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